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Methoxy-phenyl-amino-2-thiazoles, their amides and their methods of preparation

SOCIÉTÉ DE RECHERCHES INDUSTRIELLES S O R I, based in France (Côte-d'Or).

Applied for on 22 March 1967 at 09.55 in Dijon.

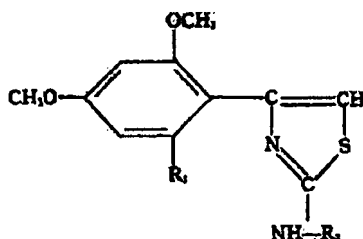
Granted by decree of 16 April 1968.

(Official Industrial Property Gazette n° 21, 24 May 1968).

(Patent, the granting of which was postponed on enforcement of Article 11, § 7, of the law of 5 July 1844 amended by the law of 7 April 1902).

The present invention relates to new chemical compounds characterised by the combination of a methoxy-phenol radical and an amino-thiazole radical. The invention relates more particularly to dimethoxy-2'-4'-phenyl-4-amino-2-thiazoles, trimethoxy-2'-4'-6'-phenyl-4-amino-2-thiazoles and various corresponding amides.

The methoxy-phenyl-amino-thiazoles according to the invention meet the general formula:

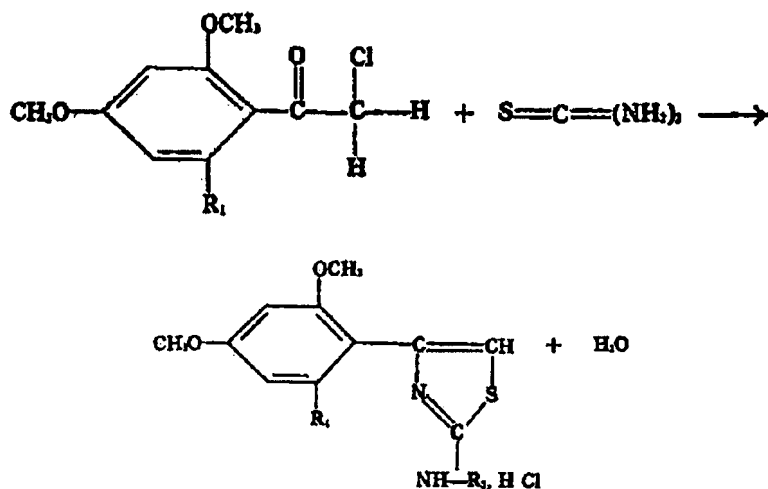


R₁ being a hydrogen or a methoxy group, R₂ being a hydrogen or a R - C = O- group deriving, by way of example, from an aliphatic, acetic, propionic, or aromatic, benzoic, trimethoxy-benzoic, cinnamic, parachloro-phenoxy-acetic acid etc.

The preparation of such compounds, according to the invention, is based on a more general and in itself known preparation process consisting of forming a thiazole radical by reaction of a molecule of thio-urea on a chloro-aceto radical. A hydrochloride and a molecule of water are thus obtained.

With regard to one of the compounds according to the invention, a molecule of a methoxy-chloro-acetophenone is reacted on a molecule of thio-urea, in solution preferably in an alcohol solvent such as ethanol, which gives a molecule of methoxy-phenyl-amino-thiazole in hydrochloride form and a molecule of water.

The reaction is as follows:



Generally, the method of preparation is as follows:

Thio-urea dissolved in approximately 150 ml of ethanol for example is introduced into a three-necked flask. It is heated to 70 – 80 degrees; all the thio-urea is soluble.

Methoxy-chloro-acetophenone dissolved in 500 ml of ethanol is added gradually using a dropping funnel and reflux boiling is carried out for 5 hours. Crystallisation is carried out for a rest period of 24 hours in the refrigerator. The white crystalline mass obtained is amino-thiazole in hydrochloride form. This mass is purified by dissolving in absolute ethanol and reprecipitation by anhydrous ether.

The hydrochlorides are in a white crystalline form; they are soluble in water and in ethanol but insoluble in ether.

The corresponding bases can be obtained by dissolving the hydrochloride in distilled water and precipitating by addition of sodium carbonate to saturation up to pH 8. The separated product is purified by redissolving in alcohol and reprecipitation by water.

These bases are in a form of white crystals soluble in alcohol and in ether but insoluble in water.

Examples of the preparation of these compounds according to the invention will now be described in detail, that is in A the preparation of dimethoxy and trimethoxy, and then in B the preparation of some corresponding amides.

A. (Dimethoxy-2'-4'-phenyl)-4-amino-2-thiazole.

7.612 g (0.10 mole) of thio-urea are introduced into a three-necked flask in approximately 150 ml of ethanol. It is heated to 70 – 80 degrees. When all the thio-urea has dissolved, 21.5 g (0.10 mole) of ω -chloro-dimethoxy-2,4-acetophenone in approximately 500 ml of ethanol are added gradually. Reflux boiling, then crystallisation enable 24.40 g of dimethoxy-2'-4'-phenyl-4-amino-2-thiazole, i.e. a yield equivalent to 89.3% theory, to be obtained after purification.

Analysis: $\text{C}_{11}\text{H}_{13}\text{ClN}_2\text{O}_2\text{S}$: 272.8.

Calculated (%):

C: 48.44; H: 4.77; N: 10.27.

Found (%):

C: 48.37; H: 4.80; N: 10.20.

Its melting point, measured on the Maquenne block, is 204 degrees C.
The base obtained from the hydrochloride according to the process described above has the empirical formula:

$C_{11}H_{12}O_2N_2S$: 236.30.

Calculated (%):

C: 55.93; H: 5.08; N: 11.86.

Found (%):

C: 55.56; H: 5.07; N: 11.70.

The melting point for this base is measured on the Maquenne block at 102 degrees C.

(Trimethoxy-2'-4'-6'-phenyl)-4-amino-2-thiazole.

7.612 g (0.10 mole) of thio-urea are introduced into a three-necked flask in approximately 150 ml of ethanol. It is heated to 70 – 80 degrees. When all the thio-urea has dissolved, 24.4 g (0.10 mole) ω -chloro-trimethoxy-2,4,6-acetophenone in approximately 500 ml of ethanol are added gradually. Reflux boiling, then crystallisation enable 28.85 g of trimethoxy-2'-4'-6'-phenyl-4-amino-2-thiazole hydrochloride, i.e. a yield equivalent to 93.5% theory, to be obtained after purification.

Analysis: $C_{12}H_{15}ClN_2O_3S$: 302.8.

Calculated (%):

C: 47.5; H: 4.95; N: 9.25.

Found (%):

C: 46.37; H: 4.89; N: 9.1.

Its melting point, measured on the Maquenne block, is 240 degrees C.

The base obtained from the hydrochloride according to the process described above has the empirical formula:

$C_{12}H_{14}N_2O_3S$: 266.30.

Calculated (%):

C: 54.13; H: 5.26; N: 10.2.

Found (%):

C: 54.02; H: 5.43; N: 9.65.

The melting point of this base is measured on the Maquenne block at 218 degrees C.

B. Regarding the preparation of the corresponding amides, two general processes can be used according to the nature of the amide sought:

1 Aliphatic acid amides:

Amidification by boiling to vapour for two hours of the acid anhydride and methoxy-phenyl-amino-thiazole in base form. Crystallisation, more or less complete, is obtained by resting for 24 hours in the refrigerator.

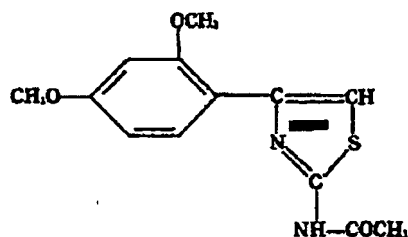
2 Amides of aromatic acids:

Amidification by condensation in a water bath at 60 degrees C for 2 hours of a solution in pyridine of methoxy-phenyl-amino-thiazole and the chloride corresponding to the selected acid. This solution, cooled to room temperature, is treated by an excess of water. The amide precipitates in the form of white crystals.

If during precipitation by water the amide obtained is resinous, it is necessary to decant and replace the water by a 10% solution of hydrochloric acid in order to separate the amide in its crystalline form.

As non-limiting examples according to these general processes can be cited:

(Dimethoxy-2'-4'-phenyl)-4-acetamido-2-thiazole.



Empirical formula: $C_{13}H_{14}N_2O_3S$.

Molecular weight: 278.355.

Preparation - 23.6 g (0.1 mole) of (dimethoxy-2'-4'-phenyl)-4-amino-2-thiazole base and 47.5 g (0.4 mole) of acetic anhydride are treated as described in the preparation method for amides of aliphatic acids.

After purification by dissolving in acetone and reprecipitation by water, 12.70 g of the amide, i.e. 45.5 % theory, are obtained.

This compound occurs in the form of white crystals, the melting point of which, measured on the Maquenne block, is 260 degrees C. It is soluble in acetone but insoluble in ethyl acetate, alcohol, ether and water.

Analysis:

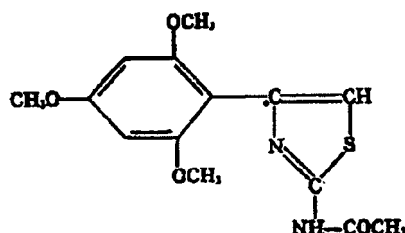
Calculated (%):

C: 56.20, H: 5.04; N: 10.06.

Found (%):

C: 56.20; H: 4.94; N: 10.06.

(Trimethoxy-2'-4'-6'-phenyl)-4-acetamido-2-thiazole.



Empirical formula: $C_{14}H_{15}N_2O_4S$.

Molecular weight: 307.372.

Preparation - 26.62 g (0.1 mole) (trimethoxy-2'-4'-6'-phenyl)-4-amino-thiazole base and 47.5 g (0.4 mole) of acetic anhydride are treated as previously.

Purification is carried out by dissolving the crystalline mass in ethyl acetate and reprecipitation in petroleum ether. 14.50 g of amide, i.e. a yield equivalent to 47.2 % theory, are obtained.

This amide occurs in a white crystalline form, the melting point of which is 198 degrees C on the Maquenne block. It is soluble in alcohol and ethyl acetate but insoluble in water and petroleum ether.

Analysis:

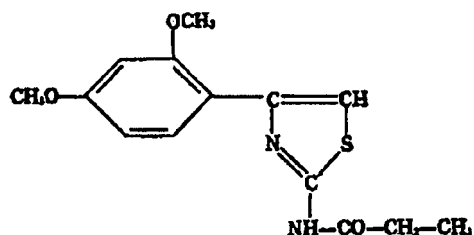
Calculated (%):

C: 54.4; H: 5.52; N: 9.11.

Found (%):

C: 54.63; H: 5.39; N: 9.18.

(Dimethoxy-2'-4'-phenyl)-4-propionamido-2-thiazole.



Empirical formula: $C_{14}H_{16}N_2O_3S$.

Molecular weight: 292.38.

Preparation - 23.6 g (0.1 mole) of (dimethoxy-2'-4'-phenyl)-4-amino-2-thiazole base and 44 g (0.4 mole) propionic anhydride are treated as previously.

Since precipitation by cooling is not complete due to the solubility of the amide in propionic anhydride, it is necessary to treat the filtrate with approximately 500 ml of water to precipitate this part remaining in solution.

For purification, the precipitate is dissolved in ethyl acetate and reprecipitated by petroleum ether. 13.3 g of amide, i.e. 45.7% of the theoretical yield, are obtained.

This amide occurs in the form of white crystals, the melting point of which is 177 degrees C on the Maquenne block. It is soluble in ethyl acetate and alcohol, and insoluble in petroleum ether and water.

Analysis:

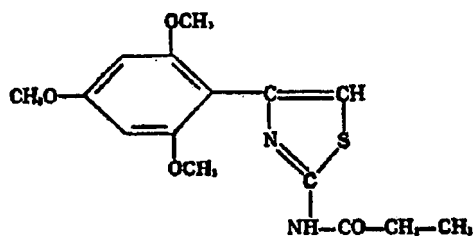
Calculated (%):

C: 57.4; H: 5.50; N: 9.61.

Found (%):

C: 57.22; H: 5.63; N: 9.66.

(Trimethoxy-2'-4'-6'-phenyl)-4-propionamido-2-thiazole.



Empirical formula: $C_{15}H_{18}N_2O_4S$.

Molecular weight: 322.40.

This compound is obtained according to the same method of preparation from (trimethoxy-2'-4'-6'-phenyl)-4-amino-2-thiazole and propionic anhydride.

It has the same characteristics as the previous compound with the exception of the melting point which is 105 degrees C.

Analysis:

Calculated (%):

C: 55.90; H: 5.59; N: 8.71.

Found (%):

C: 54.92; H: 5.77; N: 8.48.

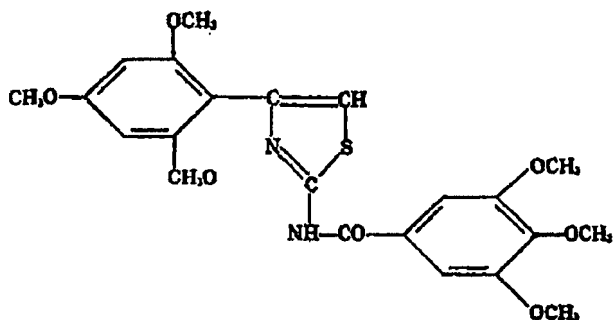
(Trimethoxy-2'-4'-6'-phenyl)-4-(trimethoxy-3'-4'-5'-benzamido)-2-thiazole.

(See formula below)

Empirical formula: $C_{22}H_{24}N_2O_7S$.

Molecular weight: 460.52.

Preparation 26.62 g (0.1 mole) of (trimethoxy-2'-4'-6'-phenyl)-4-amino-2-thiazole are dissolved in 200 ml approximately of anhydrous pyridine by shaking for a few moments.



Reheating of the reaction medium by progressive addition of 23.07 g (0.1 mole) of 3,4,5 trimethoxy-benzoyl chloride is moderated by cooling the flask. The solution turns a dark red colour. It is treated as specified above in the general method for the synthesis of amides of aromatic acids.

The purification operation comprises successive washes with:

100 ml of 10% sulphuric acid, then: 100 ml of 10% sodium carbonate, and finally with distilled water.

These washes are followed by dissolving in ethyl acetate, then reprecipitation by petroleum ether. 19.50 g of amide, i.e. 42.4% of the theoretic yield, are thus obtained.

This amide occurs in the form of white crystals, the melting point of which, measured on the Maquenne block, is 206 degrees C. These crystals are soluble in alcohol and ethyl acetate, but insoluble in water and petroleum ether.

Analysis:

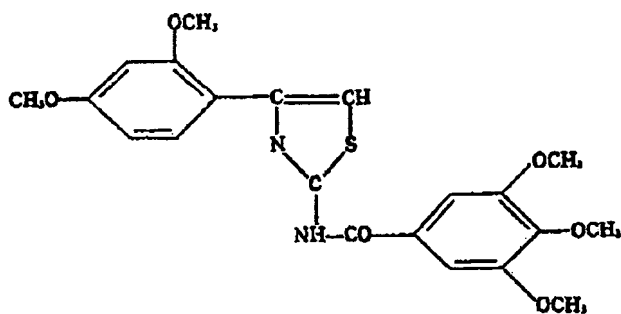
Calculated (%):

C: 57.38; H: 5.25; N: 6.08.

Found (%):

C: 56.19; H: 5.17; N: 6.82.

(Dimethoxy-2'-4'-phenyl)-4-(trimethoxy-3''-4''-5''-benzamido)-2-thiazole.



Empirical formula: $C_{21}H_{22}N_2O_6S$.

Molecular weight: 430.52.

This compound is obtained according to the same method of preparation as the previous derivative from (dimethoxy-2'-4'-phenyl)-4-amino-2-thiazole and 3-4-5-trimethoxy-benzoyl chloride.

Purification differs in the fact that it is dissolved in alcohol to reprecipitate by petroleum ether.

This amide is isolated in yellow-beige crystals; it has the same properties as its 2'-4'-6' trimethoxylate homolog with the exception of the melting point which is 198 degrees C.

Analysis:

Calculated (%):

C: 58.58; H: 5.15; N: 6.50.

Found (%):

C: 57.50; H: 5.13; N: 5.88.

(Dimethoxy-2'-4'-phenyl)-4-cinnamido-2-thiazole.

(See formula below)

Empirical formula: $C_{20}H_{18}O_3N_2S$.

Molecular weight: 366.30.

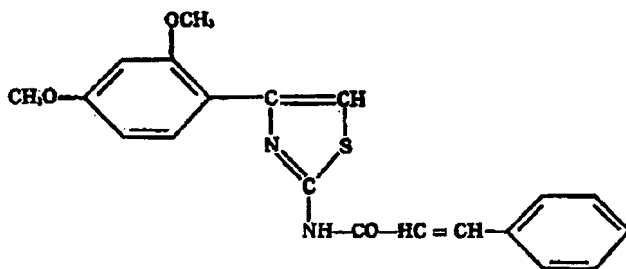
This amide is prepared according to the general method of preparation for amides of aromatic acids from (dimethoxy-2'-4'-phenyl)-4-amino-2-thiazole and cinnamoyl chloride.

Its purification is carried out by dissolving in ethyl acetate and reprecipitation in petroleum ether. Its melting point is 219 degrees C measured on the Maquenne block.

It meets the general characteristics of the compounds defined previously.

Analysis:

Calculated (%):

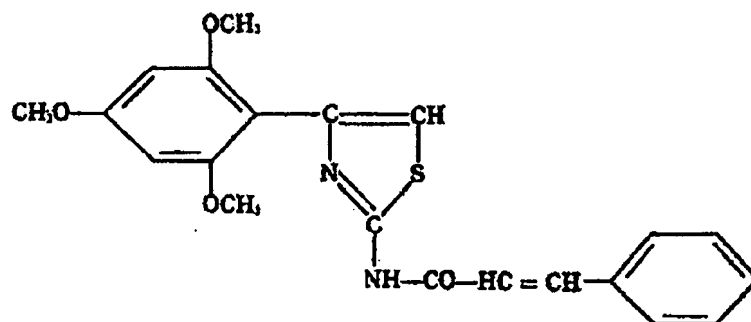


C: 65.6; H: 4.91; N: 7.70.

Found (%):

C: 65.13; H: 5.05; N: 7.68.

(Trimethoxy-2'-4'-6'-phenyl)-4-cinnamido-2-thiazole.



Empirical formula: $C_{21}H_{20}O_4N_2S$.

Molecular weight: 396.30.

Prepared according to the same protocol as its dimethoxylate homolog described above, this amide differs from the previous one by a melting point which is 214 degrees C.

Analysis:

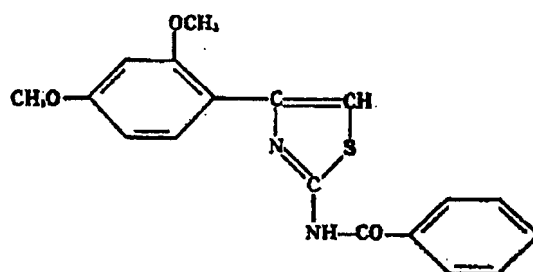
Calculated (%):

C: 63.4; H: 5.32; N: 7.09.

Found (%):

C: 62.07; H: 5.07; N: 7.10.

(Dimethoxy-2'-4'-phenyl)-4-benzamido-2-thiazole.



Empirical formula: $C_{18}H_{16}O_3N_2S$.

Molecular weight: 340.30.

This amide is prepared according to the general method of preparation common to the preceding derivatives, from (dimethoxy-2'-4'-phenyl)-4-amino-2-thiazole and benzoyl chloride.

Its melting point, measured on the Maquenne block, is 180 degrees C.

Analysis:

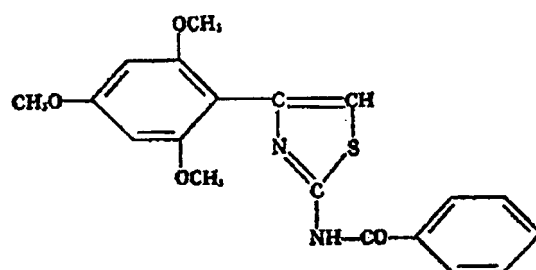
Calculated (%):

N: 8.23.

Found (%):

N: 8.27.

(Trimethoxy-2'-4'-6'-phenyl)-4-benzamido-2-thiazole.



Empirical formula: $C_{19}H_{18}O_4N_2S$.

Molecular weight: 370.30.

This amide is prepared under the same conditions as its above-mentioned homolog, with the difference that its purification is obtained by dissolving in alcohol and reprecipitation with water.

Its melting point, measured on the Maquenne block, is 198 degrees C.

Analysis:

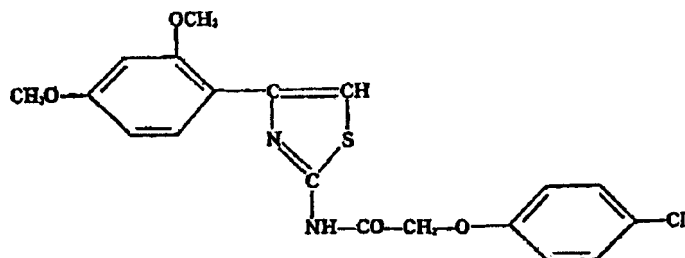
Calculated (%):

N: 7.56; C: 61.60; H: 4.86.

Found (%):

N: 7.64; C: 61.40; H: 4.91.

(Dimethoxy-2'-4'-phenyl)-4-(para-chlorophenoxyacetamido)-2-thiazole.



Empirical formula: $C_{19}H_{17}ClO_4N_2S$.

Molecular weight: 450.80.

This amide is prepared from dimethoxy-2'-4'-phenyl)-4-amino-2-thiazole and para-chloro-phenoxy-acetyl chloride according to the general method described in regard to the amides of aromatic acids.

Its purification is obtained by dissolving in ethyl acetate and reprecipitation in petroleum ether.

Its characteristics are common to all the derivatives described above.

Its melting point, measured on the Maquenne block, is 165 degrees C.

Analysis:

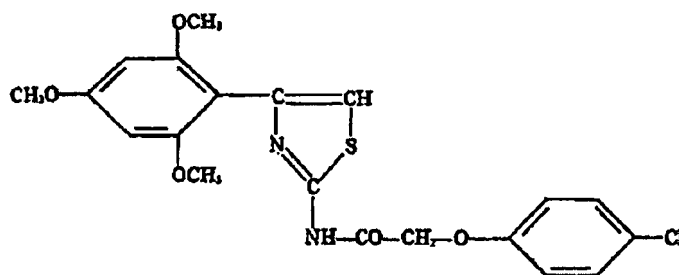
Calculated (%):

C: 56.20; H: 4.19.

Found (%):

C: 56.20; H: 4.13.

(Trimethoxy-2'-4'-6'-phenyl)-4-para-chlorophenoxyacetamido)-2-thiazole



Empirical formula: $C_{20}H_{19}ClO_5N_2S$.

Molecular weight: 435.80.

Prepared according to the same protocol as its dimethoxylate homolog described above, this amide differs from the previous one by a melting point which is 117 degrees C.

Analysis:

Calculated (%):

C: 55.30; H: 4.38.

Found (%):

C: 56.82; H: 4.32.

The infrared spectra determined on the di- and tri-methoxy-phenyl-amino-thiazoles and some of the corresponding amides have common points which enable them to be characterised.

In particular vibration brands [sic] common to all the compounds can be recognised:

At around 3030 cm^{-1} and 2420 cm^{-1} (aromatic cycles);

Between 1250 and 1260 cm^{-1} (methoxy groups);

Between 835 and 840 cm^{-1} (di 2',4' substitution or tri 2',4',6' substitution);

Between 1530 and 1520 cm^{-1} (thiazole cycle).

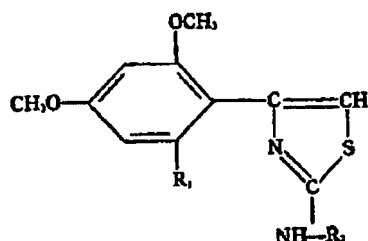
The amino compounds also have bands: between 1610 and 1620 (amine group).

The amides have bands: between 1600 and 1650 cm^{-1} (secondary amide group).

SUMMARY

The invention relates to new chemical compounds resulting from the combination of a methoxy-phenyl radical and an amino-thiazole radical, and more particularly from dimethoxy-2'-4'-phenyl-4-amino-2-thiazoles, trimethoxy-2'-4'-6'-phenyl-4-amino-2-thiazoles and different corresponding amides.

The methoxy-phenyl-amino-thiazoles according to the invention correspond to the general formula:



R_1 being a hydrogen or a methoxy group,

R_2 being a hydrogen or a $R-C=O$ - group deriving, by way of example, from an aliphatic, acetic, propionic, or aromatic, benzoic, trimethoxybenzoic, cinnamic, parachlorophenoxyacetic acid.

The preparation of such compounds, according to the invention, is based on a more general and in itself known preparation process consisting of forming a thiazole radical by reaction of a molecule of thio-urea on a chloro-aceto radical. A hydrochloride and a molecule of water are thus obtained.

With regard to one of the compounds according to the invention, a molecule of a methoxy-chloro-acetophenone is reacted on a molecule of thio-urea, in solution preferably in an alcohol solvent such as ethanol, which gives a molecule of methoxy-phenyl-amino-thiazole in hydrochloride form and a molecule of water.

Generally, the method of preparation is as follows:

Thio-urea dissolved in approximately 150 ml of ethanol for example is introduced into a three-necked flask. It is heated to 70 – 80 degrees; all the thio-urea is soluble.

The methoxy-chloro-acetophenone dissolved in 500 ml of ethanol is added gradually using a dropping funnel and reflux boiling is carried out for 5 hours. Crystallisation is carried out for a rest period of 24 hours in the refrigerator.

The white crystalline mass obtained is amino-thiazole in hydrochloride form. This mass is purified by dissolving in absolute ethanol and reprecipitation by anhydrous ether.

The hydrochlorides are in a white crystalline form; they are soluble in water and in ethanol, but insoluble in ether.

The corresponding bases can be obtained by dissolving the hydrochloride in distilled water and precipitating by addition of sodium carbonate to saturation up to pH 8. The separated product is purified by redissolving in alcohol and reprecipitation by water.

These bases are in a form of white crystals soluble in alcohol and in ether but insoluble in water.

Amidification is obtained depending on the circumstances by boiling methoxy-phenyl-amino-thiazole in base form in the presence of an aliphatic acid anhydride or by condensation in pyridine at a temperature of around 60 degrees of methoxy-phenyl-amino-thiazole and an aromatic acid chloride.

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By proxy:
Michel LALOE